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Constitutional Mosaicism for a Chromosome 9 Inversion Resulting in Recombinant Aneusomy in an Offspring

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We report on a case of constitutional mosaicism for a large pericentric inversion of chromosome 9 in a man whose daughter had recombinant aneusomy resulting in partial 9q duplication and partial 9p deletion. At age 6 months, the girl was evaluated because of dysmorphic congenital animal features and developmental delay. Chromosomal analysis on this infant showed a derivative chromosome 9 which was later determined to be a recombinant chromosome with trisomy of 9q34.1→qter and monosomy of pter→9p24. Chromosomal analysis in her father showed the presence of two cell lines; 75% of lymphocytes had a 46,XY pattern, and 25% had a 46,XY,inv(9)(p24q34.1) karyotype. The infant's physical findings represent a composite of the reported cases of both trisomy 9q34.1→qter and monosomy pter→9p24. The infant's father was phenotypically and cognitively normal. This case broadens the spectrum of reported cases of mosaicism for an autosomal structural rearrangement generating unbalanced gametes, and further supports the tenet that constitutional mosaicism has clinical relevance for genetic counseling. Am. J. Med. Genet. 69:360–364, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: human chromosome 9; constitutional mosaicism; pericentric inversion; recombinant aneusomy; cerebral atrophy; psychomotor retardation

INTRODUCTION

Balanced mosaic chromosomal rearrangements are perceived to be rare in the general population. Mosaicism for balanced chromosomal rearrangements has been reported in couples experiencing multiple spontaneous abortions or infertility [Castle and Bernstein, 1988; Farrell, 1991]. In a review by Farrell [1991], 6 cases of mosaic balanced reciprocal translocations were ascertained among 284 reciprocal translocations in 80,806 specimens. Each of these translocations was found in a significant proportion of cells analyzed. As pointed out by the author, the prevalence of mosaic structural rearrangements could not be estimated from these data without knowledge of laboratory referral distribution patterns. Nevertheless, documentation of these cases was important in providing evidence of the occurrence of mosaic structural rearrangements. In other studies where patients were ascertained by more diverse criteria (including phenotypic abnormalities, multiple miscarriages, and detection of abnormalities in the products of conception from a spontaneous abortion), similar frequencies of mosaicism for balanced chromosomal rearrangements were found, which varied from 0.03–0.3 per 1,000 cases analyzed [Saura et al., 1987; Kleczkowska et al., 1990; Opheim et al., 1995].

The rates of mosaic balanced reciprocal translocations have also been determined from prenatal amniocentesis samples, with estimated frequencies of <0.02–0.1 per 1,000 samples; these rates may approximate the true frequency in the general population [Bui et al., 1984; Hsu and Perlis, 1984; Worton and Stern, 1984; Hook and Cross, 1987; Hsu et al., 1996]. In the largest collaborative study to date, Hsu et al. [1996] identified 13 cases of mosaic balanced reciprocal translocations in 179,663 amniocenteses, confirming 3 cases of balanced mosaicism in the newborn infants. This study also identified 4 cases of mosaic inversions, with 2 of the cases confirmed in the newborn infants.

These studies documenting balanced chromosomal mosaicism indicates that although they are relatively uncommon, mosaic balanced chromosomal rearrangements in the population may represent a true genetic counseling concern, particularly when providing recur-

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rence risks to couples who have had multiple miscarriages or a chromosomally unbalanced offspring. Germline mosaicism for balanced chromosomal translocations or inversions has been implicated as a causative factor in couples experiencing multiple spontaneous abortions [reviewed in Castle and Bernstein, 1988 Kleczkowska et al., 1990; Farrell, 1991]. In addition, cases of chromosomally unbalanced offspring have been previously reported to occur for individuals with mosaicism for balanced chromosomal translocations [reviewed in Gardner et al., 1994; Opheim et al., 1995].

To date, there have been no reported cases of individuals with mosaicism for a chromosomal inversion who have had chromosomally unbalanced offspring. Such cases should exist as long as the cell line with the inversion contributes to gonadal tissue, and recombination events result in chromosomally unbalanced gametes. Here we report on such a case, whereby a girl with recombinant aneusomy (partial 9q duplication and partial 9p deletion) has a father with constitutional mosaicism for a large pericentric inversion of chromosome 9.

CLINICAL REPORT

The patient is a Latin-American girl born at term gestation to her 25-year-old G1P1 mother by cesarean section because of cephalopelvic disproportion, and failure of labor progression. Apgar scores were 8 and 9 at 1 and 5 min, respectively. Her birth weight was 3,388 g (65th centile), length was 52 cm (90th centile), and head circumference was 37 cm (>90th centile). The pregnancy was uncomplicated, and ultrasonographic examinations at 6 weeks and 7 months of pregnancy were normal. The infant had an uncomplicated neonatal course.

During infancy she had no significant medical illnesses, and her only medical problem was blocked lacrimal ducts. She fed well on a soy-based formula. However, she had significant gross motor delay and hypotonia. At age 6 months (Fig. 1), she was unable to roll over, crawl, or sit. She reached for objects, but would not grasp them. She had no head support in an upright position, and she could not lift her head when lying prone. Her growth parameters were normal. Her physical findings included brachycephaly, a metopic ridge with suture synostosis, small anterior fontanel, low-set posteriorly-angulated ears with simplified helices, downslanting palpebral fissures, flattened midface, small beaked nose, high-arched palate, thin upper lip, small mouth, micrognathia, wide-spaced nipples, and extra transverse finger creases. There was global hypotonia, and tendon reflexes were absent.

Diagnostic evaluations included echocardiography, which showed a small secundum atrial septal defect and mild asymmetric hypertrophy of the interventricular septum. A brain MRI scan showed a small, atrophic, structurally normal brain with dilated extracerebral spaces (Fig. 2). A hearing evaluation by auditory brainstem response testing was normal. Ophthalmologic examination showed bilateral oblique muscle dysfunction and a secondary exotropia as well as moderate hypermetropia, but no structural abnormalities.

The parents were not consanguineous, and both were phenotypically and cognitively normal. A paternal uncle of the patient died in childhood from complications related to a thoracolumbar neural tube defect. The family history was otherwise unremarkable.

Fig. 1. Patient at age 6 months.

Cytogenetic Analyses

Chromosome analyses were performed on peripheral blood lymphocytes from the patient and both parents. This demonstrated an abnormal chromosome 9 in the child, which following analysis of her father's chromo-

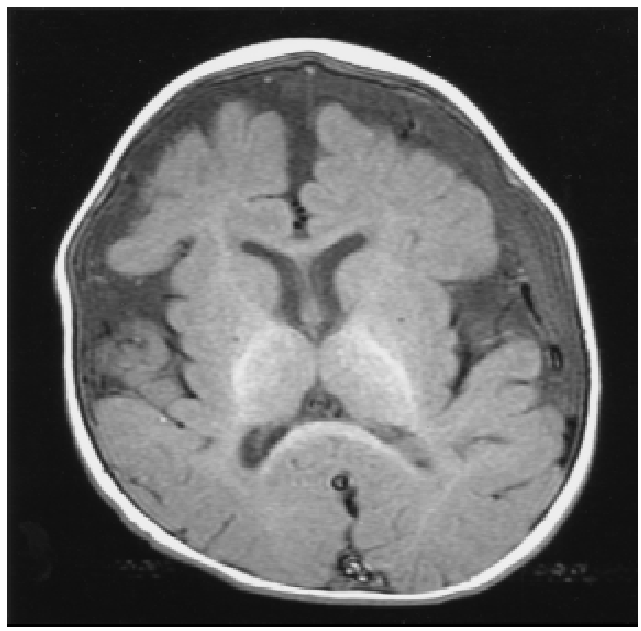

Fig. 2. Patient's brain MRI scan at age 6 months. The scan demonstrates brain atrophy and gross dilatation of the extracerebral spaces over both cerebral hemispheres. Fluid is present in the subarachnoid space on the right, with the suggestion that much of the fluid on the left is in the subdural space. No congenital anomalies or delays in myelination are noted.

somes, was determined to be a recombinant chromosome [rec(9)dup(9q)inv(9)(p24q34.1)pat] resulting in trisomy of 9q34.1→qter and monosomy of pter→9p24 (Fig. 3). Her mother had normal chromosomes, but her father had two cell lines in peripheral blood lymphocytes, with 75% of lymphocytes having a 46,XY pattern and 25% of lymphocytes having a 46,XY,inv(9)(p24q34.1) karyotype (Fig. 3). His parents were unavailable for cytogenetic studies.

DISCUSSION

The child described here has clinical findings of both trisomy 9q34.1→qter and monosomy pter→9p24 (Table I). The clinical manifestations of these two aneusomic conditions listed in Table I are a compilation from previous reports [Hoo et al., 1979; Allderdice et al., 1983; Houdou et al., 1987; Spinner et al., 1993]. In addition, the patient described here has a previously unreported finding of cerebral and cerebellar atrophy, with fluid in the subdural and subarachnoid spaces (Fig. 2).

The child's father is mosaic in peripheral blood lymphocytes for a large pericentric inversion of chromosome 9. The mosaicism must extend to his gonadal tissue because the child inherited a duplication-deficiency of the ends of chromosome 9, as would be expected from a recombination event within an inversion loop during meiotic pairing. The child's father represents the first documented case of a mosaic inversion carrier producing a recombinant aneusomic offspring.

There are no reports of patients with similar recombinant aneusomy for chromosome 9. Two patients with

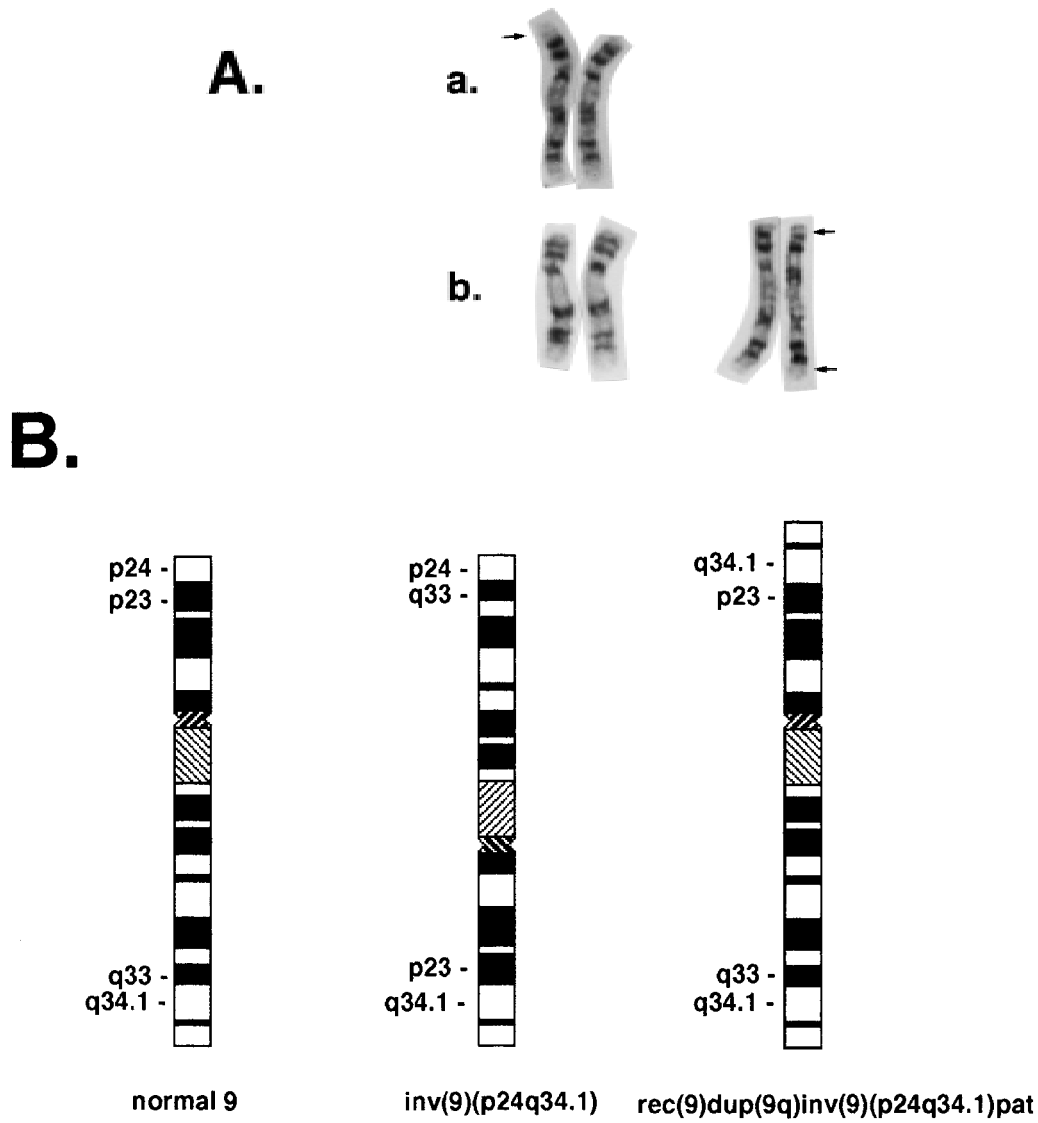

Fig. 3. **A:** Partial GTG-banded karyotypes on (**a**) the patient and (**b**) her father. In the patient, the recombinant chromosome 9 is on the left (arrow) and the normal chromosome 9 is on the right. In her father, the normal pair of chromosomes 9 is on the left (75% of lymphocytes), and the pair of chromosomes 9 with a pericentric inversion is on the right (25% of lymphocytes). Breakpoints in the inverted chromosome in b are indicated by arrows. **B:** Ideogram of GTG-banded chromosome 9. The normal chromosome 9 is on the left, the inversion 9 is in the middle, and the recombinant duplication-deficiency chromosome 9 is on the right.

TABLE I. Clinical Findings of del(9)(pter→p24) and dup(9)(q34.1→qter) Compared With the Present Case

Feature	del(9) (pter→p24)	dup(9) (q34.1→qter)	Present case
Short stature (proportionate)	+	+	
Trigonocephaly/metopic ridge	+	+	+
Low-set ears	+	+	+
Ear dysplasia	+		+
Upslanting palpebral fissures	+		
Prominent eyes	+		+
Strabismus	+	+	+
Blocked/absent nasolacrimal duct	+		+
Flat nose	+		
Anteverted nares	+		
Long philtrum	+		+
Cupid-bow mouth shape	+	+	+
Micrognathia	+	+	+
High-arched palate	+		+
Short neck	+		
Excess nuchal skin	+		
Widely spaced nipples	+		+
Dolichomesophalangia	+	+	+
Psychomotor retardation	+	+	+
Dolichocephaly		+	
Frontal bossing		+	+
Facial asymmetry		+	
Ear asymmetry		+	+
Deep-set eyes		+	
Short palpebral fissures		+	
Downslanting palpebral fissures		+	+
Beaked nasal profile		+	+
Prominent nasal bridge		+	+
Small mouth		+	+
Excess digital creases		+	+
Camptodactyly		+	+
Long toes		+	+
Hypotonia		+	+
Congenital heart defects		+	+
Intestinal abnormalities		+	
Cerebellar anomalies		+	
Genital anomalies (males)		+	
Brain atrophy			+

more segmental aneusomy than the child described here had 46,XX,rec(9),dup(9q),inv(9)(p22q32)pat [Mattei et al., 1980; Sonoda et al., 1991]. Both of these patients had the phenotype of partial trisomy 9q, but in contrast to the child reported here, they had few, if any, of the findings of partial monosomy 9p. Another child with even more severe aneusomy (46,XX,–9,+i(9q)) was described in conjunction with significant prenatal ethanol exposure [Sanders et al., 1984], but it was difficult to sort out which findings in this child were due to 9p deletion and 9q duplication vs. those due to fetal alcohol exposure. Therefore, no prior reported cases offer a meaningful comparison with the child reported here.

Structural chromosomal mosaicism in a parent can be unbalanced or balanced, but in either case may have significant reproductive implications, due to the high likelihood that chromosomally abnormal gametes will be produced. Unbalanced mosaicism has been found in a parent deemed to have mild features of Langer-Giedion syndrome [Naritomi and Hirayama, 1989] or Smith-Magenis syndrome [Zori et al., 1993], after a child was born with the typical microdeletion syndrome. Mosaicism for balanced constitutional chromosomal rearrangements in a phenotypically normal parent, as in the case reported here, has been ascertained after a couple has had multiple spontaneous abortions or aneusomic offspring. Therefore, all cases of structural aneusomy in a child or spontaneous abortus should raise the concern that a parent may in fact be mosaic for a chromosomal rearrangement.

For cases of aneusomy in an offspring or fetal tissue, it is problematic if structural mosaicism in a parent is not detected because the abnormal cell line is missed by routine cytogenetic analysis of peripheral blood lymphocytes. It seems particularly important to exclude low-level mosaicism if the aneusomic offspring has a chromosome pattern resulting from a probable meiotic recombination event, as was the case in the child presented here. Screening 20 metaphase cells for a rearrangement detects mosaicism of $\geqslant$14% at a 95% confidence level [Hook, 1977]. In the majority of reported series [reviewed in Opheim et al., 1995], when present in the blood, the frequency of cells in a mosaic state carrying a structural rearrangement ranges from 10–55%. It would seem that this level of analysis would be adequate to detect most similar cases of structural mosaicism. However, such series may be biased against the ascertainment of lower-level mosaics, and do not take into account cases of mosaic structural rearrangements detected only in cells other than peripheral blood lymphocytes. Therefore, when low-level mosaicism in a parent is suspected based on the offspring's pattern of aneusomy, additional cells should be screened and thought given to analyzing other parental tissues.

It would be ill-advised to screen <20 cells to exclude structural mosaicism, since even the current practice of screening 20 cells is not adequate to detect all cases of mosaicism. And even if mosaicism is not detected in 20 cells, genetic counseling for chromosomally normal parents, with a prior aneusomic offspring or fetal loss, should always address the theoretical possibility of recurrence in a future pregnancy resulting from gonadal mosaicism.

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